FACTSHEET

RISK ASSESSMENT METHODOLOGY

Year 2001

National Toxicology Program

P.O. Box 12233
MD: A3-01
Research Triangle Park
N.C. 27709-2233

headquartered at the

NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES

NATIONAL INSTITUTES OF HEALTH

For further information contact the NTP Liaison Office at:
919-541-0530
Fax: 919-541-0295
liaison@starbase.niehs.nih.gov

Risk assessment involves the synthesis of large amounts of diverse data to arrive at a decision concerning the plausibility and magnitude of hazards posed by environmental agents. The NTP initiative on methodology for risk assessment has focused on the development of a strong linkage between laboratory methods, objective analysis methods, and mechanism-based mathematical models. Mechanism-based mathematical models are used to quantify the sequence of events that start with chemical exposure and end with overt toxicity. Models, whose designs are biologically based, allow researchers to link a broad array of experimental findings in ways that are both biologically logical and useful in risk assessment for defining dose-response relationships, making species comparisons, and assessing inter-individual variability. Statistical and mathematical models are being developed for other NIEHS and NTP initiatives, such as human exposure assessment, genomics and proteomics, to improve the utility of human and animal data for use in risk assessments.

Several models are now complete and bear noting. EPA is using a model developed for 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD, dioxin) as part of an ongoing mechanistically based risk assessment. This model and one developed for 1,3-butadiene include the best characterizations available for the pharmacological and biochemical effects of these compounds. Mechanistically based models are also being developed and applied to NTP data (e.g. naphthalene, methyleugenol, AIDS therapeutics) to provide a better means for analyzing and interpreting bioassay results. Inclusion of physiologically based pharmacokinetic models (PBPK) in NTP technical reports is becoming routine, and such information should give guidance to regulatory agencies interested in extrapolation of data across species. Models are under development for multiple cancer endpoints, developmental endpoints and reproductive toxicity.

The NIEHS toxicokinetics faculty evaluates the appropriateness of a biologically based pharmacokinetic models for each chemical selected for NTP study. If a credible and potentially useful model can be constructed, then a study is designed to collect the appropriate data. The NTP's effort in risk assessment is closely tied to its growing initiatives in mechanism-based toxicology. This linkage provides opportunities to improve priority setting, use mechanistic information to establish risk or safety, clarify dose-response relationships in the "low dose" range, select the most appropriate experimental systems for estimating risk, and develop science-based models for specific subpopulations (e.g. age, gender, genetic predisposition, ethnicity, etc.). Information about models and projects related to risk assessment is available at http://www.niehs.nih.gov.

For further information, contact: Dr. Christopher Portier, NIEHS,
P.O. Box 12233, MD A3-06, Research Triangle Park, NC 27709
Phone: 919-541-4999

Selected Reading

1. Melnick RL, Sills RC, Portier CJ, Roycroft JH, Chou BJ, Grumbein SL, Miller RA. Multiple organ carcinogenicity of inhaled chloroprene (2-chloro-13-butadiene) in F344/N rats and B6C3F$_1$ mice and comparison of dose-response with 1,3-butadiene in mice. Carcinogenesis 1999;20(5):867-78.

2. Andersen M, Conolly R, Faustman E, Kavlock R, Portier C, Sheehan D, Wier P, Ziese L. Quantitative mechanistically based dose response modeling with endocrine active compounds. Environmental Health Perspectives 1999;107(4):631-38.

3. Portier C. Risk ranges for various endpoints following exposure to 2,3,7,8-TCDD. Food Additives and Contaminants 2000;17(4):335-346.

4. Halmes NC, Roberts SM, Tolson JK, Portier CJ. Re-evaluating cancer risk estimates for short-term exposure scenarios. Toxicological Sciences 2000;58.